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Increased vitamin B12 in heart failure with reduced ejection fraction: A novel marker of disease severity and mortality

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Abstract
Aim: The relationship between elevated vitamin B12 levels and liver damage is well-established, but its association with the severity of heart failure (HF) remains unclear. This study aimed to investigate the prognostic importance of vitamin B12 levels according to disease severity in HF patients with reduced left ventricular ejection fraction (HFrEF).
Material and Methods: Two hundred and three consecutive patients with HFrEF were enrolled in this study. Patients were divided into advanced and non-advanced HF groups based on specific criteria and the primary endpoint was all-cause mortality, which was prospectively assessed. Cox proportional hazards regression analyses were conducted to identify independent predictors of mortality.
Results: Of the study patients, 75 (36.9%) had advanced, while 128 (63.1%) had non-advanced HF. The advanced group had significantly higher serum vitamin B12 levels compared to the non-advanced group ($p<0.001$). Serum vitamin B12 level of > 707.8 pg/mL had a sensitivity of 78.3% and specificity of 76.1% in predicting all-cause mortality (area under the curve=0.863, 95% CI 0.806-0.920, $p<0.001$). Kaplan-Meier analysis demonstrated that patients with vitamin B12 levels > 707.8 pg/mL had significantly lower survival rates ($p < 0.001$). In Cox regression analysis, vitamin B12 emerged as an independent predictor of death.
Discussion: Elevated serum vitamin B12 levels in HFrEF patients are associated with advanced HF, increased ALT and GGT levels, indicating a cardiohepatic syndrome, and independently predict higher all-cause mortality risk.

Keywords
Heart Failure, Vitamin B12, Hepatic Congestion, Mortality, Biomarker

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Introduction

Heart failure is a clinically significant health issue affecting approximately 1-2% of the adult population in developed countries. It is a major global health problem, causing significant mortality and hospitalization among adults [1]. Furthermore, the presence of comorbid conditions complicates the treatment process, with anemia being a significant problem that prolongs hospitalization. The incidence of anemia among individuals with HF ranges from 4% to 61%, with iron deficiency being the primary cause [2].

The prevalence of vitamin B12 deficiencies in HF patients remains uncertain, with studies reporting conflicting results [2-4]. Recent research has identified a connection between plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker for systemic congestion, and vitamin B12 levels in HF [5].

Vitamin B12 has been recognized as a potential marker for liver cell damage, as it can be released into the bloodstream from damaged liver cells [6]. Heart failure can cause disruptions in liver oxygenation due to hypotension, decreased blood oxygen levels, and hepatic congestion [7]. This hepatocyte injury can lead to the release of stored vitamin B12 into the bloodstream, resulting in increased serum levels [7-9]. While this increase has been demonstrated in acute HF [10], the difference in vitamin B12 levels according to HF stage is less clear in chronic HF.

This study aimed to investigate the association between vitamin B12 levels and HF severity and mortality in advanced and non-advanced chronic HF patients with reduced ejection fraction.

Material and Methods

Study population

The study population consisted of consecutive chronic HF patients admitted to the Department of Cardiology, between January 2017 and February 2019. The inclusion criteria were age 18 years or older, chronic stable HF with echocardiographic evidence of reduced left ventricular ejection fraction (≤40%), and experiencing symptoms corresponding to a functional class of New York Heart Association (NYHA) I-IV. Exclusion criteria included acute decompensated HF, prior myocardial infarction and myocarditis within the last six months, active infection, hypertrophic and restrictive cardiomyopathy, non-cardiac liver failure, renal failure requiring dialysis, malignancies, connective tissue-inflammatory and autoimmune diseases, pregnancy, vegan or vegetarian dietary patterns, and receiving vitamin B12 replacement therapy within the last six months.

The patients were classified into two groups based on the 2018 European Society of Cardiology Advanced HF Status Statement criteria: advanced HF group and non-advanced HF group [11]. The advanced HF group was characterized by severe and persistent HF symptoms according to the NYHA functional classification system of class III or IV and significant cardiac dysfunction with a left ventricular ejection fraction of ≤ 30% [11]. Data on demographic characteristics, physical examination findings, laboratory results, NYHA functional classes, and echocardiographic evaluations were obtained from the hospital's electronic medical record system for all patients. The study's primary endpoint was all-cause mortality, which was prospectively evaluated at regular intervals via outpatient visits or telephone interviews until December 2019.

Of the 245 patients screened, 26 had their vitamin B12 levels and other laboratory data measured on different days, 9 tested positive for anti-hepatitis C antibody or showed reactivity to hepatitis B surface antigen, and 7 had left ventricular assist devices, leaving a total of 203 patients available for this study (Figure 1).

Laboratory assessments

Peripheral venous blood samples were obtained from the antecubital vein and collected into standardized tubes containing EDTA for complete blood count analysis using the XE-1200 instrument (Sysmex, Kobe, Japan). Routine liver function tests that included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and gamma-glutamyl transferase (GGT) were obtained at the time of admission, as were plasma levels of vitamin B12 and NT-proBNP. Vitamin B12 and NT-proBNP levels were determined using the Beckman Coulter Access Immunoassay Systems. The manufacturer's reference interval for vitamin B12 was 211–911 pg/mL.

Echocardiographic evaluation

Transthoracic echocardiography was performed on all patients using a commercially available device (VIVID 7, GE Medical Systems, Milwaukee, WI) using a 2.5 MHz probe. Left ventricular ejection fraction (LVEF) were measured using a modified Simpson's method during the same visit when blood samples were collected to assess vitamin B12 levels. Tricuspid annular plane systolic excursion (TAPSE) value less than 17mm was defined as right HF accompanying left ventricular dysfunction. Echocardiography was performed to assess the diameter of the inferior vena cava (IVC), and greater than 2.1 cm was defined as IVC dilatation [12].

Statistical Analysis

All analyses were performed using the SPSS 26 software package (IBM Corp., Armonk, NY). The Kolmogorov-Smirnov test assessed the normal distribution of the variables. Variables were expressed as frequencies, percentages (%), means (±standard deviation), and medians (interquartile range), as appropriate. The Chi-square test compared categorical variables. Inter-group comparisons of continuous variables were performed using Student's t-test (for parametric data) or the Mann–Whitney U test (for non-parametric data). A univariate linear regression model was initially constructed using all clinical, echocardiographic, and laboratory variables with significant correlations with vitamin B12 ($p<0.05$). Subsequently, for predicting vitamin B12 levels, all variables included in the univariate linear regression were entered into a multivariate linear regression model using the backward elimination method. Receiver operating characteristic curve (ROC) analysis was performed to assess the cut-off value of vitamin B12 for predicting all-cause mortality. Kaplan-Meier analysis was used to estimate survival over the follow-up period for categories of independent variables, and the log-rank test was used to compare survival functions calculated according to different factors. Predictive Cox regression models were created using significant variables from the log-rank test. For the model obtained, crude and multivariable-adjusted hazard

ratios and 95% confidence intervals were determined for each variable. A two-sided p-value < 0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of Türkiye Yüksek İhtisas Training and Research Hospital (Date: 2019-02-06, No: 2019-0012).

Results

The study included 203 consecutive patients with chronic stable HF, 75 (36.9%) with advanced HF, and 128 (63.1%) with non-advanced HF. Most patients (84.2%) were male, with a mean age of 52 years (range 19-70). The mean follow-up time was 20.1±8.1 months. No significant differences were found between the advanced and non-advanced groups in terms of age (p=0.309), gender (p=0.467), etiology of HF (p=0.510), hypertension (p=0.593), and diabetes mellitus (p=0.232). Characteristics of the groups are presented in Table 1.

Vitamin B12 deficiency was similar between advanced and non-advanced HF groups [8 patients (10.7%) vs. 21 patients (16.4%), respectively; p=0.390]. On the contrary, serum vitamin B12 levels were found to be significantly higher in the advanced HF group compared to the non-advanced group [829 pg/mL (137-2000) vs. 363.3 pg/mL (148.3-991), p<0.001]. The prevalence of concomitant right HF in advanced HF patients was determined to be higher compared to the non-advanced HF group [64 patients (85.3%) vs. 53 patients (41.4%), p<0.001]. Higher levels of vitamin B12 were observed in advanced HF

Table 1. Baselines characteristics of the non-advance HF and advanced HF patients

Variables	Non-advanced (n=128)	Advanced (n=75)	p value
Demographic and clinical characteristics			
Age, year	51.5 (19.0-70.0)	52.0 (21.0-70.0)	0.309
Female gender, n(%)	22 (17.2%)	10 (13.3%)	0.467
Hypertension, n(%)	63 (49.2%)	34 (45.3%)	0.593
Diabetes mellitus, n(%)	39 (30.5%)	29 (38.7%)	0.232
Ischemic etiology, n(%)	59 (46.1%)	31 (41.3%)	0.510
Vitamin B12 deficiency, n(%)	21 (16.41%)	8 (10.67%)	0.390
Cardiac device, n(%)	114 (89.1%)	70 (93.3%)	0.313
Right-sided heart failure, n(%)	53 (41.4%)	64 (85.3%)	<0.001
Death during follow-up, n(%)	10 (7.8%)	22 (29.3%)	<0.001
IVC dilatation, n(%)	32 (25%)	68 (90,6%)	<0.001
NYHA functional class*	2.6±0.3	3.4±0.2	<0.001
Biochemical values			
Urea (mg/dL)	40.0 (15.0-98.0)	53.0 (20.0-181.0)	<0.001
Creatinine (mg/dL)	0.9 (0.4-1.9)	1.0 (0.5-3.7)	0.008
eGFR (mL/min/1.73 m2)	83.0 (34.0-194.0)	78.0 (12.0-144.0)	0.047
Uric acid* (mg/dL)	7.2±4.6	8.5±2.9	0.351
Sodium (mEq/L)	140.0 (126.0-147.0)	137.0 (123.0-147.0)	<0.001
Potassium* (mEq/L)	4.5±0.5	4.3±0.6	0.047
AST (U/L)	21.0 (9.0-202.0)	33.0 (10.0-2167.0)	<0.001
ALT (U/L)	21.0 (9.0-348.0)	30.0 (9.0-2743.0)	<0.001
Direct bilirubin (mg/dL)	0.3 (0.07-4.2)	0.7 (0.1-15.7)	<0.001
Indirect bilirubin (mg/dL)	0.49 (0.01-2.80)	0.73 (0.09-23.0)	<0.001
NT-proBNP (ng/L)	1170.5 (113.0-14823.0)	10582.0 (675.0-35000.0)	<0.001
Medications			
Beta-blocker, n(%)	110 (85.9%)	66 (88.0%)	0.676
ACEi/ARB/ARNI, n(%)	120 (93.8%)	71 (94.7%)	0.789
Digoxin, n(%)	16 (12.5%)	17 (22.7%)	0.058
MRAs, n(%)	97 (75.8%)	64 (85.3%)	0.105
Furosemide or thiazide, n(%)	100 (78.1%)	67 (89.3%)	0.044
Hematological and hematinic parameters			
Hemoglobin* (g/dL)	13.9±1.7	13.2±1.8	0.384
MCV (fL)	86.0 (61.2-98.6)	85.2 (62.7-98.5)	0.447
Vitamin B12 (pg/mL)	363.3 (148.3-991.0)	829.0 (137.0-2000.0)	<0.001
Folic acid (ng/mL)	9.4 (2.3-17.0)	9.0 (2.6-20.0)	0.653
Echocardiographic characteristics			
LVEF (%)	20.5 (10.0-36.0)	20.0 (8.0-32.0)	<0.001
LVEDD (mm)	62.0 (43.0-91.0)	66.0 (41.0-105.0)	0.024
TAPSE (mm)	17.0 (7.0-26.0)	13.0 (7.0-23.0)	<0.001

* shows normally distributed data

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor, ALT: alanine aminotransferase, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitor, AST: aspartate transaminase, eGFR: glomerular filtration rate, IVC: inferior vena cava, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, MCV: mean corpuscular volume, MRAs: mineralocorticoid receptor antagonists, NT-proBNP: N terminal pro hormone of brain natriuretic peptide, TAPSE: tricuspid annular plane systolic excursion

patients with concomitant right HF compared to those without right HF [879.6 pg/mL (137.0-2000.0) vs. 803.9 pg/mL (400.0-1205.0), respectively; p=0.037]. However, a similar significant difference was not found in the non-advanced group (p=0.056). In the univariate analysis, several variables including LVEF (r = -0.399, p<0.001), TAPSE (r = -0.423, p<0.001), NT-proBNP (R = 0.748, p<0.001), ALT (R = 0.460, p<0.001), GGT (R = 0.554, p<0.001), direct bilirubin (R = 0.504, p<0.001), and indirect bilirubin (R = 0.342, p<0.001) levels, exhibited significant correlations with vitamin B12 levels in patients with HFrEF. However, in multivariate analysis, NT-proBNP (p<0.001), ALT (p=0.002), and GGT (p<0.001) all displayed positive correlations with vitamin B12 levels, while conversely, the LVEF showed a negative association with vitamin B12 (p=0.006) (Table 2).

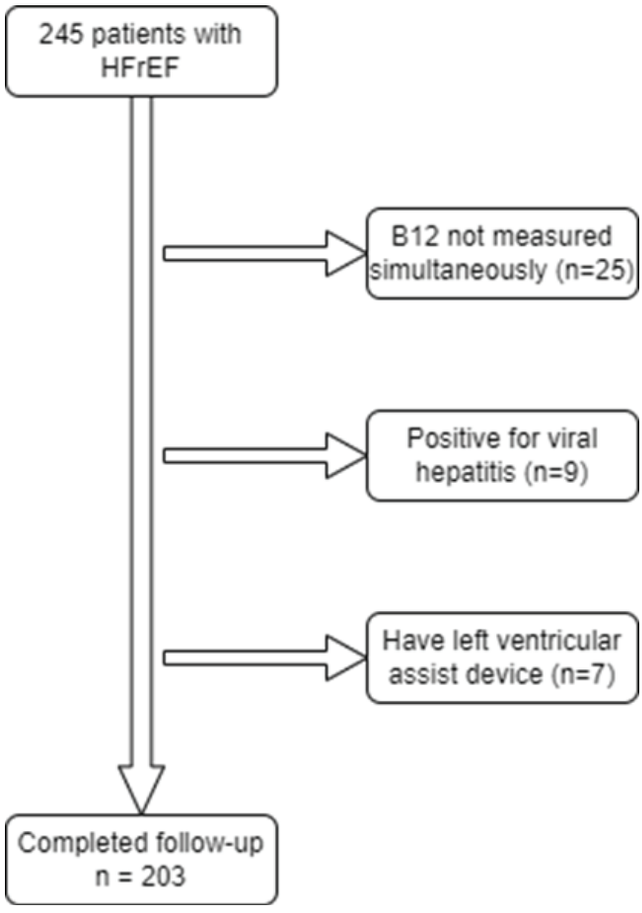

Figure 1. Study Flowchart. The diagram describes the protocol used for the enrollment of patients with HFrEF in the present study. HFrEF, heart failure with reduced ejection fraction

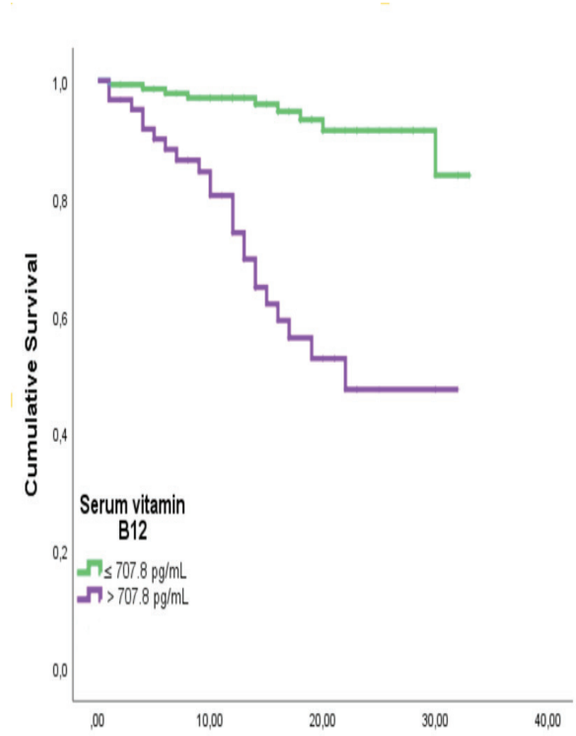

Figure 2. Kaplan–Meier survival curves for the all HFrEF patients with high and low serum B12 levels. Abbreviation: HFrEF, heart failure with reduced ejection fraction

Table 2. Significant multivariate correlates of vitamin B12 in HFrEF patients

	Multivariate regression coefficient (95% CI)	p value
NT-proBNP	0.024 (0.018-0.029)	<0.001
Left ventricular ejection fraction	-7.154 (-12.269- -2.039)	0.006
ALT	0.201 (0.077-0.324)	0.002
Direct bilirubin	21.801 (-13.069-56.670)	0.219
Indirect bilirubin	-20.532 (-50.220-9.156)	0.174
GGT	0.576 (0.257-0.895)	<0.001
TAPSE	-1.927 (-9.515-5.660)	0.617

Abbreviations: ALT; alanine aminotransferase, GGT; gamma glutamyl transferase, NT-proBNP; N terminal prohormone of brain natriuretic peptide, TAPSE; tricuspid annular plane systolic excursion

Table 3. Univariate and multivariate cox regression analysis of predictors of mortality in HFrEF patients

Variables	Univariate regression coefficient (95% CI)	p-value	Multivariate regression coefficient (95% CI)	p-value
Age	1.022 (0.982-1.063)	0.287		
Male gender	0.660 (0.245-1.777)	0.411		
Diabetes mellitus	2.647 (1.160-6.042)	0.021	2.374 (1.033-5.454)	0.042
Advanced HF	44.059 (5.936-327.004)	<0.001	22.919 (2.881-182.342)	0.003
Vitamin B12	6.869 (2.916-15.193)	<0.001	1.107 (1.000-1.302)	0.008
NT-proBNP	11.318 (2.653-48.280)	0.001		
LVEF	3.697 (1.566-8.730)	0.003		
TAPSE	43.7 (1.321-1450.5)	0.034		

Abbreviations: CI; confidence interval, HF: heart failure, HFrEF: heart failure with reduced ejection fraction, LVEF: left ventricular ejection fraction, NT-proBNP: N terminal prohormone of brain natriuretic peptide, TAPSE: tricuspid annular plane systolic movement

ROC curve analysis showed that a serum B12 level of 707.8 pg/mL had a sensitivity of 78.3% and specificity of 76.1% in predicting all-cause mortality, with an area under the curve (AUC) of 0.863 (95% CI: 0.806-0.920, p<0.001). In Kaplan-Meier analysis, the survival rate was significantly lower in patients with a serum vitamin B12 level > 707.8 pg/mL than in patients with a serum vitamin B12 level ≤ 707.8 pg/mL (62.3% vs. 93.7%, p<0.001) (Figure 2).

Mortality data were available for all patients. During the follow-up period, the overall mortality rate was 15.76% (n=32). Furthermore, the levels of vitamin B12 were higher in the deceased patients compared to the surviving patients [909.0 pg/mL (587.0-2000.0) vs. 438.5 pg/mL (148.3-2000.0), respectively; p<0.001].

Kaplan-Meier analysis was used to estimate survival during the follow-up period based on various independent variables. Variables of diabetes mellitus, advanced HF, vitamin B12, NT-proBNP, LVEF, and TAPSE that showed significant associations with mortality in the Log-Rank test, along with age and gender, were further evaluated using Cox proportional hazards regression models to determine their independent predictive value for mortality. Multivariate analysis revealed a significant association between mortality and various factors, including diabetes mellitus (adjusted hazard ratio [aHR] = 2.374, 95% confidence interval [CI] 1.033-5.454, p=0.042), advanced HF (aHR = 22.919, 95% CI 2.881-182.342; p=0.003), and serum vitamin B12 levels (aHR = 1.107, 95% CI 1.000-1.302; p=0.008) per 1 unit increase, as demonstrated in Table 3. The results of the Cox regression analysis indicated that higher levels of vitamin B12 were associated with an increased risk of mortality in patients with HFrEF.

Discussion

This study demonstrated the emergence of vitamin B12 as an independent predictor of mortality in patients with HFrEF. In fact, increased vitamin B12 levels were more prevalent in the advanced HF group, suggesting its potential relevance in disease progression.

Previous reports indicate a positive correlation between serum vitamin B12 levels and the severity of HF [13,14]. An early study by Rachmilewitz et al. [9] first investigated the use of serum cyanocobalamin to indicate hepatic injury in HF. Their study focused on 28 patients with chronic congestive HF and significant hepatomegaly. They reported a considerable decrease in serum cyanocobalamin levels in cases where compensation was achieved. However, this study did not report on changes in vitamin B12 levels after treatment and stabilization of the patients, which is important for understanding the relationship between vitamin B12 and stable chronic HF at different stages. Numerous studies have demonstrated that advanced HF is associated with a cholestatic liver enzyme profile, characterized by elevated levels of ALT, AST, and GGT in the bloodstream, a manifestation of the cardiohepatic syndrome [15, 16]. Argan et al. [17] have reported higher levels of vitamin B12 in patients with chronic stable HFrEF compared to the general population. This elevation was associated with clinical signs of right HF and slight increases in direct bilirubin levels, suggesting the presence of cardiohepatic syndrome. Additionally, our study revealed a correlation between higher vitamin B12 levels and liver function abnormalities, such as elevated ALT and GGT levels. These findings suggest that higher vitamin B12 levels could serve as a potential marker for detecting the presence of cardiohepatic syndrome, a condition that becomes more prominent as HF progresses.

Several potential mechanisms have been proposed to explain HF's increased serum cobalamin levels. One hypothesis is that liver dysfunction, the most extensive reservoir of vitamin B12 in the body, could disrupt cobalamin storage, releasing cobalamin from hepatocytes. Another possibility is that endothelial dysfunction resulting from hepatic congestion due to elevated venous pressure may contribute to reduced synthesis of transport proteins and diminished binding capacity of vitamin B12 [18]. Zafarullah et al. [10] conducted a study to investigate the serum levels of vitamin B12 in patients hospitalized with decompensated HF. They reported that patients with biventricular failure exhibited elevated serum vitamin B12 levels during their initial hospitalization. However, after receiving diuretic treatment and experiencing a reduction in systemic congestion, the vitamin B12 levels decreased by approximately 30% upon discharge [10]. Moreover, we found that patients in the advanced HF group had a higher rate of diuretic usage and showed dilatation of the IVC, indicating a greater degree of systemic congestion [19, 20]. These findings further strengthen the association between HF severity, the level of congestion, and elevated vitamin B12 levels.

Elevated levels of vitamin B12 in the bloodstream have been recognized as an early indication of an underlying severe condition [21]. Supporting this notion, a study conducted by Soohoo et al. [22] demonstrated a correlation between high plasma concentrations of vitamin B12 and an increased mortality risk among hemodialysis patients. Similarly, elevated vitamin B12 levels are frequently observed in hepatocellular carcinoma and hematological malignancies and are associated with mortality in these diseases [23,24]. However, the association between elevated vitamin B12 levels and mortality in HF patients has not been established.

In our study, we found that elevated levels of vitamin B12 not only provided insights into the severity of HF but also emerged as an independent predictor of mortality. These results suggest that vitamin B12 can be a potential biomarker for monitoring HF progression. Therefore, during the clinical evaluation of HF patients, clinicians should be alert to the accompanying increase in vitamin B12 levels, and closer monitoring of these patients may be warranted.

Limitation

Our study has several limitations. Firstly, the study had a retrospective design. Another limitation is the relatively smaller sample size in the advanced HF group compared to the non-advanced HF group, which could have been addressed by having an equal number of patients in both groups to strengthen our results. Furthermore, we did not assess hepatic endothelial dysfunction or monitor vitamin B12 transporters such as transcobalamin-II. Transcobalamin II is crucial in transporting vitamin B12 from the gastrointestinal system to various tissues, including the liver. At the same time, transcobalamin-I (or haptocorrin) is involved in reverse-transporting vitamin B12 from tissues back to the liver [25]. These values would have helped us determine whether transporter synthesis is affected

in advanced-stage HF and the underlying reasons for the elevated serum cobalamin levels.

Conclusion

Elevated serum vitamin B12 levels in HFrEF patients are associated with advanced HF, increased ALT, and GGT levels, indicating a cardiohepatic syndrome and independently predicting higher all-cause mortality risk.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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